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ORIGINAL ARTICLE

Prospective Study

Long-term antiviral efficacy of entecavir and liver histology improvement in Chinese patients with hepatitis B virus-related cirrhosis

Yan Xu, Yong-Gui Zhang, Xu Wang, Wen-Qian Qi, Shao-You Qin, Zhen-Hua Liu, Jian Jiao, Jiang-Bin Wang

Yan Xu, Yong-Gui Zhang, Xu Wang, Wen-Qian Qi, Shao-You Qin, Zhen-Hua Liu, Jian Jiao, Jiang-Bin Wang, Department of Gastroenterology, China-Japan Union Hospital, Jilin University, Changchun 130033, Jilin Province, China

Author contributions: Xu Y, Zhang YG and Wang JB designed the research; Wang X and Liu ZH performed the research; Zhang YG, Qi WQ and Jiao J contributed new reagents or analytic tools; Xu Y and Qin SY analyzed the data; Xu Y and Zhang YG wrote the paper.

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Correspondence to: Jiang-Bin Wang, Professor, Department of Gastroenterology, China-Japan Union Hospital, Jilin University, No. 126 Xiantai Dajie, Changchun 130033, Jilin Province, China. yongguizhangcn@126.com
Telephone: +86-431-84995303
Fax: +86-431-84641026

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Abstract

AIM: To evaluate the clinical outcomes of 240-wk treatment with entecavir (0.5 mg) in Chinese nucleoside-naive patients with cirrhosis.

METHODS: A total of 204 nucleoside-naive patients with compensated (n = 96) or decompensated (n = 108) hepatitis B virus (HBV)-induced cirrhosis at the Department of Gastroenterology of the China-Japan Union Hospital (Jilin University, Changchun, China) who were treated with entecavir (0.5 mg) for 240 wk were enrolled in this study. Liver biopsy samples obtained from 38 patients prior to treatment (baseline) and at week 240 were evaluated by different independent histopathologists. Efficacy assessments included the proportions of patients who achieved an HBV DNA level < 500 copies/mL, the association of interleukin-28B genetic variation with antivirus therapy, clinical outcomes, and histologic improvement. Changes in liver disease severity were analyzed, and liver histologic evaluation was performed in 38 patients with paired biopsies. Student t tests were used to compare the means of continuous variables between the groups, and the proportions of patients who achieved the endpoints were compared using the χ^2 test.

RESULTS: At week 240, 87.5% of the patients with compensated cirrhosis and 92.6% of the patients with decompensated cirrhosis achieved a HBV DNA level < 500 copies/mL. Three patients had genotypic entecavir resistance within the 240-wk period. No significant association was observed between virologic response and interleukin-28 genotype (CT, 88.2% *vs* CC, 90.6%). The proportion of patients with Child-Pugh

class A disease was significantly increased at week 240 (68%) from the baseline (47%; $P < 0.01$). The proportion of patients with Child-Pugh class B disease was significantly decreased at week 240 (25%) from the baseline (39%; $P = 0.02$). In the patients with paired liver biopsies, the mean reduction in the Knodell necroinflammatory score from the baseline was 3.58 ± 1.03 points (7.11 ± 1.80 *vs* 3.53 ± 1.35, $P < 0.01$). The mean reduction in Ishak fibrosis score from the baseline was 1.26 ± 0.64 points (5.58 ± 0.50 *vs* 4.32 ± 0.81, $P < 0.01$).

CONCLUSION: Entecavir is an effective treatment option for patients with HBV-related compensated or decompensated cirrhosis that can result in sustained virologic suppression and histologic improvement.

Key words: Decompensated cirrhosis; Hepatic function; Histologic improvement; Knodell histologic activity index score; Nucleoside analog

Core tip: Entecavir is a potent antiviral agent that is effective and safe for the treatment of chronic hepatitis B. However, data on its clinical benefits in patients with cirrhosis, especially in long-term treatment, are limited. The aims of this prospective study were to evaluate the antiviral efficacy and clinical outcomes of entecavir treatment for 240 wk in nucleoside-naive Chinese patients with chronic hepatitis B, and compensated or decompensated cirrhosis.

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INTRODUCTION

Chronic hepatitis B (CHB) remains a serious global public health problem, with an estimated 350-400 million people affected worldwide[1]. Such patients are at increased risk of developing cirrhosis, hepatic decompensation, and hepatocellular carcinoma (HCC)[2]. In the absence of treatment, 15%-20% of patients develop cirrhosis within five years[3,4]. Patients who subsequently progress to decompensated cirrhosis have a poor prognosis, with a five-year survival rate of only 14%-28% compared with 84% for patients with compensated cirrhosis[5,6]. Elevated serum hepatitis B virus (HBV) DNA levels are an independent risk factor of progression to cirrhosis, hepatic decompensation, HCC, and death[7,8]. Conversely, sustained reductions in viral load associated with antiviral therapy are strongly correlated with decreased risk of disease progression and improvements in liver histology and clinical signs or symptoms[9,10].

Multiple clinical studies have demonstrated that nucleos(t)ide analogs are effective in suppressing viral replication and reducing disease progression in patients with HBV-related cirrhosis[11-13]. In a randomized clinical trial, long-term lamivudine treatment (median duration, 32.4 mo) significantly reduced overall disease progression (increase in Child-Pugh score, hepatic decompensation, or HCC) compared with placebo (7.8% *vs* 17.7%, $P = 0.001$) in patients with hepatitis B e antigen-positive CHB and advanced fibrosis/compensated cirrhosis[12]. In contrast, data on clinical outcomes with nucleos(t)ide analogs in patients with decompensated cirrhosis are limited.

Entecavir is a potent antiviral agent that has been shown to be effective and safe for the treatment of CHB[14-17]. A subanalysis of phase Ⅲ clinical data found that 57%-59% of patients with CHB and advanced liver fibrosis/cirrhosis experienced improvements in terms of Ishak fibrosis score at 48 wk of entecavir therapy[18]. More recently, the Shim *et al*[19] research group observed the clinical efficacy of one-year entecavir therapy in 55 patients with decompensated cirrhosis and found that 66% of the patients had improved Child-Turcotte-Pugh scores, which comprises individual scores for five parameters, namely total bilirubin level, serum albumin level, prothrombin time, ascites level, and hepatic encephalopathy. Patients with scores of 5 or 6, 7-9, or 10-15 were classified as having Child-Pugh class A, B, or C liver disease, respectively. Of the patients, 49% had increased Child-Turcotte-Pugh scores by ⩾ 2. Clinical trial data from patients with advanced fibrosis/cirrhosis found that after approximately six years of cumulative entecavir therapy, all ten patients showed improvement in liver histology and Ishak fibrosis score. In particular, four patients had Ishak fibrosis scores ⩽ 4 after the entecavir therapy[20].

Although the efficacy and safety of entecavir in nucleoside-naive patients without cirrhosis have been demonstrated in multiple studies, limited data are available on the clinical benefits in patients with cirrhosis. The aims of this prospective study were to evaluate the antiviral efficacy and clinical outcomes of entecavir treatment for 240 wk in nucleoside-naive Chinese patients with CHB and compensated or decompensated cirrhosis.

MATERIALS AND METHODS

Study design

This prospective study evaluated the efficacy of entecavir (Bristol-Myers Squibb, Wallingford, CT, United States) at 0.5 mg once daily for 240 wk in patients with cirrhosis. Nucleoside-naive patients ($n = 204$) with HBV-related cirrhosis who attended the Department of Gastroenterology at the China-Japan Union Hospital

(Jilin University, Changchun, China) were recruited and enrolled in the study beginning in June 2006. Diagnoses of compensated and decompensated cirrhosis were based on liver biopsy and/or clinical, radiologic, and laboratory criteria according to disease management guidelines[21]. Liver disease severity was graded according to Child-Pugh score. Patients with scores of 5 or 6, 7-9, or 10-15 were classified as Child-Pugh class A, B, or C, respectively. This study was conducted in accordance with the declaration of Helsinki. This study was conducted with approval from the Ethics Committee of Jilin University. Written informed consent was obtained from all participants.

Study population

Eligible patients were adults aged ⩾ 16 years with CHB infection (defined as hepatitis B surface antigen positive for ⩾ 6 mo with persistent detectable hepatitis B surface antigen and/or serum HBV DNA) and compensated or decompensated cirrhosis. All of the patients were nucleoside-naive prior to entecavir treatment and had serum HBV DNA levels ⩾ 500 copies/mL as measured using a PCR assay (Da An Gene Co. Ltd, Guangzhou, China; lower limit of detection, 500 copies/mL). The exclusion criteria included patients with coinfection with HIV or hepatitis A, C, D, or E viruses, and active alcohol abuse or dependence. Women who were pregnant or breastfeeding were also excluded.

Efficacy assessments

HBV DNA, interleukin (IL)-28B genotype, and serum biochemical profiles were analyzed at baseline, weeks 4 and 12 of treatment, and every 12 wk thereafter up to 240 wk of treatment. Efficacy was defined when patients achieved a HBV DNA level < 500 copies/mL (*via* PCR) at week 240. The clinical endpoint assessed was disease progression in the total study population. Disease progression was defined as an increase in Child-Pugh score of ⩾ 2, hepatic decompensation, HCC, spontaneous bacterial peritonitis, bleeding gastroesophageal varices, or death related to liver disease.

Liver biopsy samples obtained from 38 patients prior to treatment (baseline) and at week 240 were evaluated by different independent histopathologists. The proportions of patients with improvements in Knodell histologic activity index (HAI), fibrosis, and necroinflammatory scores from the baseline were assessed at week 240. Histologic improvement was defined as a decrease in Knodell necroinflammatory score of ⩾ 2 points from the baseline and no worsening of fibrosis score, or a decrease in Ishak fibrosis score of ⩾ 1 point from the baseline. Histologic worsening was defined as an increase in Knodell necroinflammatory score of ⩾ 2 points or an increase in Ishak fibrosis score of ⩾ 1 point from the baseline.

Resistance analysis

Patients with a virologic breakthrough (> 1-$\log_{10}$ increase in HBV DNA level higher than the nadir) were monitored for resistance mutations. Nucleotide sequence analysis of the HBV polymerase gene to detect genotypic entecavir resistance was performed for on-treatment samples by an independent laboratory (TaKaRa Biotechnology Co., Ltd., Dalian, China).

Safety

The incidence of adverse events, treatment discontinuation, deaths, and on-treatment alanine aminotransferase flares (defined as a serum level > 2 × baseline and > 10 × upper limit of normal) were documented. Renal impairment (defined as an elevation in serum creatinine to > 3 × upper limit of normal *vs* baseline) was also monitored. In all the patients with increased lactate serum concentrations, arterial blood gas analysis was performed immediately.

Statistical analysis

Statistical analysis was performed using SPSS v13.0 (SPSS Inc., Chicago, IL, United States). Continuous variables are expressed as mean ± SD and categorical data are expressed as proportions or percentages. The Student's *t* test was used to compare the means of the continuous variables between the groups. The proportions of patients who achieved the end points were compared using the χ^2 test. All of the tests were two-sided, and $P < 0.05$ was considered as statistically significant.

RESULTS

Patient disposition

A total of 204 patients with HBV-related cirrhosis who were treated with entecavir for 240 wk at the China-Japan Union Hospital (Jilin University, Changchun, China) beginning in June 2006 were enrolled in this study. Of these patients, 96 had compensated cirrhosis (Child-Pugh class A) and 108 had decompensated cirrhosis (Child-Pugh classes B and C). Thirty-eight patients had paired liver biopsies at baseline and week 240 of treatment. The patients were predominantly male (67%-78%), and patients in the compensated cirrhosis group were significantly younger ($P < 0.05$) (Table 1). The compensated cirrhosis group also had higher alanine aminotransferase levels and fewer patients with HBV genotype C than the decompensated cirrhosis group (both $P < 0.05$).

Virologic response

At 240 wk of treatment, 87.5% of the patients with compensated cirrhosis and 92.6% of the patients with decompensated cirrhosis had achieved serum HBV DNA levels < 500 copies/mL. No significant differences in virologic response were observed between the two groups at week 240.

IL-28 genotypes vs efficacy

The genotype distributions of rs12979860 C/T in all

Table 1 Demographics and baseline characteristics of patients

Characteristic	Compensated cirrhosis group (n = 96)	Decompensated cirrhosis group (n = 108)	P value
Age (yr)	33.4 ± 10.6	42.4 ± 14.5	< 0.05
Male	64 (67)	84 (78)	0.085
HBeAg-positive	72 (75)	46 (43)	< 0.05
HBV DNA (log_{10} copies/mL)	6.5 ± 1.3	5.6 ± 1.5	0.077
ALT (IU/L)	131.4 ± 125.7	72.5 ± 63.1	< 0.05
HBV genotype			
B	40 (42)	16 (15)	< 0.05
C	48 (50)	78 (72)	< 0.05
Other (A and D)	8 (8)	14 (13)	0.367

Data are presented as mean ± SD or n (%). ALT: Alanine aminotransferase; HBeAg: Hepatitis B e antigen; HBV: Hepatitis B virus.

the patients were analyzed. For the genotypes, the proportion of the CT genotype in the patients was 16.7% and that of the CC genotype was 83.3%. No significant association was observed between virologic response and IL-28 genotype (CT, 88.2% *vs* CC, 90.6%).

Histologic improvement

Histologic evaluation of liver biopsy samples from 38 patients with HBV-related cirrhosis indicated that 20 (52.6%) patients had a Knodell HAI score of 0-3 points at week 240 of entecavir treatment. The mean reduction in the Knodell necroinflammatory score from the baseline was 3.58 ± 1.03 points (7.11 ± 1.80 *vs* 3.53 ± 1.35, $P < 0.01$; Figure 1A).

With respect to fibrosis, 89.5% of the patients achieved improvement (⩾ 1 point decrease from the baseline) in terms of Ishak fibrosis score. The mean reduction in Ishak fibrosis score from the baseline was 1.26 ± 0.64 points (5.58 ± 0.50 *vs* 4.32 ± 0.81, $P < 0.01$; Figure 1B).

A total of 89.5% of the patients achieved improvement (decrease in Knodell necroinflammatory score of ⩾ 2 points from the baseline and no worsening of fibrosis score, or a decrease in Ishak fibrosis score of ⩾ 1 point from the baseline).

Relationship between HBV DNA level and histologic improvement

The relationships between HBV DNA level and the Knodell HAI and Ishak fibrosis scores at baseline and after entecavir treatment were analyzed by performing linear regression using data from the histology subgroup of patients (n = 38). As shown in Figure 2A, viral load at baseline was significantly correlated with Knodell HAI and Ishak fibrosis scores in the untreated patients (r = 0.880 and r = 0.876, respectively; P = 0.01). Similarly, decreases in HBV DNA level from the baseline were strongly correlated with decreases in Knodell HAI (r = 0.60; P = 0.01), but not Ishak fibrosis score (r = 0.17) at week 240 of entecavir treatment (Figure 2B).

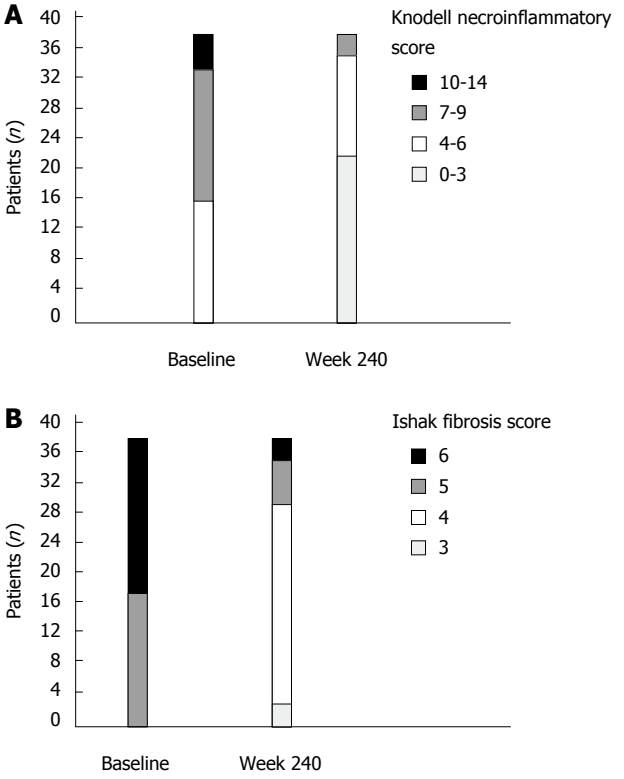

Figure 1 Improvements in liver histology at week 240 of entecavir treatment in patients (n = 38) with paired liver biopsies (baseline and week 240). A: Distribution of Knodell necroinflammatory scores at baseline and at week 240; B: Distribution of Ishak fibrosis scores at baseline and at week 240.

Clinical outcomes

The proportion of patients with disease progression in the decompensated cirrhosis group was 4.6% within the 240 wk. Three patients were found to have HCC at weeks 40, 60, and 72, and two patients had bleeding gastroesophageal varices at weeks 36 and 48. None of the patients had worsened compensated cirrhosis (Figure 3).

Liver disease severity (Child-Pugh class) at baseline, week 96, and week 240 in the total study population is shown in Figure 4. The proportion of patients with Child-Pugh class A disease significantly increased from the baseline at week 240 (47% *vs* 68%, $P < 0.01$). The proportion of patients with Child-Pugh class B disease significantly decreased from the baseline at week 240 (39% *vs* 25%, P = 0.02), with corresponding decreases occurring in the proportions of patients with Child-Pugh class C disease.

Resistance

Three patients (1.5%) experienced a virologic breakthrough during 240 wk of entecavir treatment. They had the same mutations, and resistance mutation occurred in rtM204I/V, rtL180M, and rtT184, respectively.

Safety

None of the patients discontinued treatment with

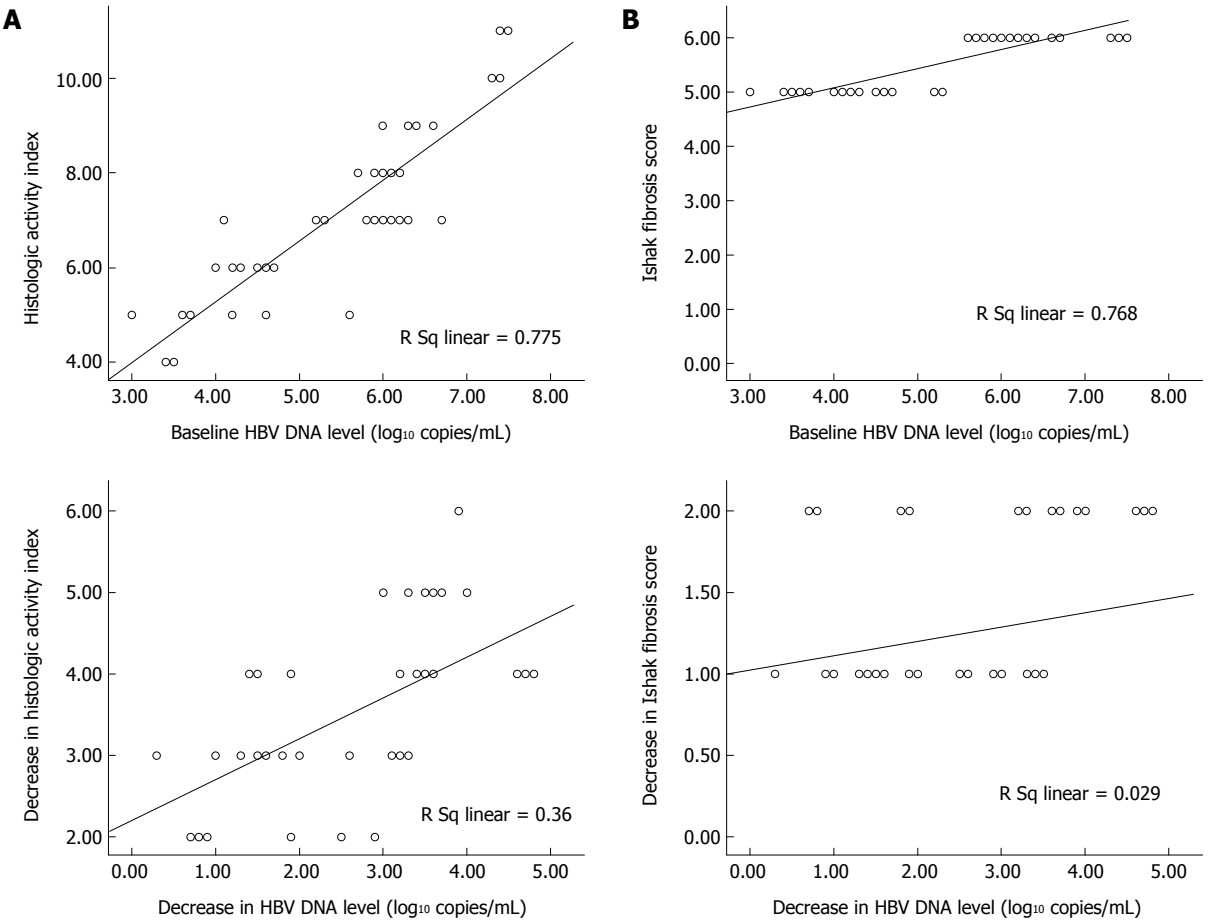

Figure 2 Relationship between hepatitis B virus DNA level and histologic improvement. A: Relationships between hepatitis B virus (HBV) DNA level and Knodell histologic activity index and Ishak fibrosis score at baseline; B: Relationships between changes from baseline in HBV DNA level and Knodell histologic activity index and Ishak fibrosis score at week 240 of entecavir treatment.

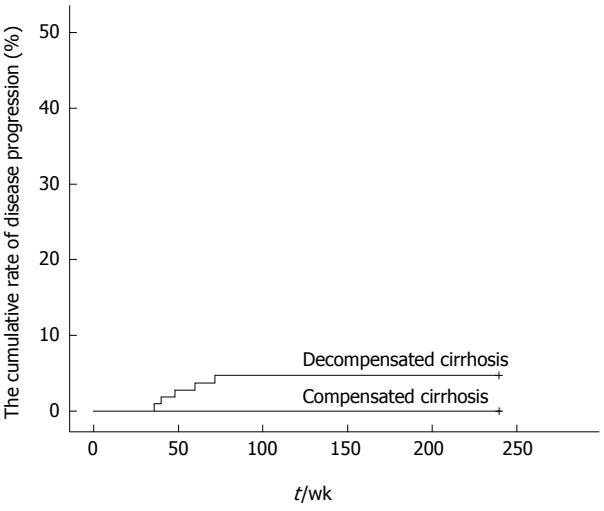

Figure 3 Proportion of patients with disease progression in compensated and decompensated cirrhosis groups.

entecavir, experienced renal function impairment, or developed lactic acidosis throughout the 240-wk period of treatment with entecavir.

DISCUSSION

Data on the efficacy and safety of entecavir in patients with CHB-related cirrhosis are limited. This prospective study demonstrates that entecavir is an effective treatment option for Chinese nucleoside-naive patients with CHB and compensated or decompensated cirrhosis. Most of the patients achieved virologic suppression (HBV DNA level < 500 copies/mL) by week 240 of therapy. Furthermore, histologic improvement was observed in most (89.5%) of the patients with paired biopsies at baseline and week 240. The most important finding is that the entecavir treatment was associated with significant improvements in hepatic functional reserve in the patients with decompensated cirrhosis.

Sustained suppression of HBV replication is recommended as a primary aim of therapy for CHB[22-24]. In this study, 88% and 93% of patients with compensated and decompensated cirrhosis, respectively, achieved an HBV DNA level < 500 copies/mL by week 240. These results confirm previous findings that demonstrated the efficacy of entecavir in nucleoside-naive patients

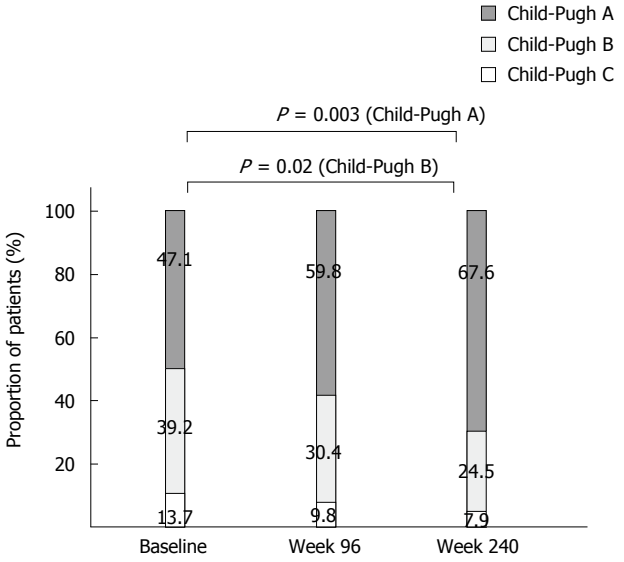

Figure 4 Improvements in Child-Pugh grade at weeks 96 and 240 of entecavir treatment in patients with compensated and decompensated cirrhosis.

and extended these findings to patients with CHB and compensated or decompensated cirrhosis.

The long-term goal of treatment for CHB is to arrest or reverse liver disease progression[22,23]. After week 240 of entecavir therapy, all of the 38 patients showed improvement in liver histology and Ishak fibrosis score. The mean change in Knodell necroinflammatory and Ishak fibrosis scores from the baseline were -1.3 and -3.5, respectively. These findings are consistent with previous studies that demonstrated histologic improvement with nucleoside analog treatment in patients with bridging fibrosis/cirrhosis[12,18,20,25,26]. Clinical trial data from ten patients with advanced fibrosis/cirrhosis (Ishak fibrosis scores, 4-6) found that after approximately six years of cumulative entecavir therapy (range: 267-297 wk), all of the patients showed improvement in liver histology and Ishak fibrosis score; mean changes in Ishak fibrosis and Knodell necroinflammatory scores from the baseline were 2.2 and 7.6, respectively. A reduction in Ishak fibrosis score to 4 or lower was observed for all four patients who had cirrhosis at baseline[20].

In a previous study of one-year entecavir treatment in Korean patients with decompensated cirrhosis, genotypic resistance to entecavir was not evaluated[7]. In contrast, comprehensive resistance monitoring of all the patients in the present study found a virologic breakthrough in three patients. These results are consistent with the low cumulative probability of genotypic entecavir resistance (0.5% at two years to 1.2% over six years) observed in clinical trials with nucleoside-naive patients without cirrhosis[27,28]. Considering that current CHB guidelines recommend long-term treatment for patients with cirrhosis[22-24], the low rate of genotypic entecavir resistance in this study provides further evidence to support the use of entecavir in patients with CHB and either decompensated or compensated cirrhosis.

Recently, genome-wide association studies have shown that several single-nucleotide polymorphisms in the IL-28B gene (*IL28B*) on chromosome 19q13, which encodes type Ⅲ interferon (IFN; also named IFN-λ3), are strongly associated with not only spontaneous and treatment-induced clearance of hepatitis V virus (HCV) infection, but also the course of HCV-related disease[29]. Moreover, our recent study also showed that *IL28B* polymorphism rs12979860 is associated with response to treatment in Chinese hepatitis C patients[30]. Considering that HBV and HCV are both hepatotropic viruses that can establish chronic infections that persist for the lifetime of the host and are sensitive to the antiviral activity of IFN-λ in cell culture models of virus replication, it might be possible that genetic variants of *IL28B* play a similar functional role during chronic HBV infection[31]. Several previous studies in different ethnic groups have suggested that *IL28B* genetic variation is associated with HBV-related disease and IFN-based treatment outcomes[32-35]. However, the present study shows that virologic response and IL-28 genotype are not significantly associated.

In conclusion, this study demonstrates that entecavir is safe and provides potent virologic suppression and improvement in overall liver disease severity in nucleoside-naive patients with HBV-related decompensated or compensated cirrhosis. Sustained virologic suppression, biochemical response, and improvements in liver histology were achieved by most of the patients throughout the 240 wk of treatment. These findings, together with a high genetic barrier to resistance, provide evidence that support the use of entecavir as a first-line treatment for patients with CHB and advanced liver disease.

COMMENTS

Background

Entecavir is a potent antiviral agent that has been shown to be effective and safe for the treatment of chronic hepatitis B (CHB). However, data on its clinical benefits in patients with cirrhosis, especially in long-term treatment, are limited.

Innovations and breakthroughs

Prospectively evaluate the antiviral efficacy and clinical outcomes of entecavir treatment for 240 wk in nucleoside-naive Chinese patients with CHB, and compensated or decompensated cirrhosis.

Applications

This study demonstrates that entecavir is an effective treatment option for Chinese nucleoside-naive patients with CHB, and compensated or decompensated cirrhosis, can result in sustained virological suppression and histological improvement.

Peer-review

The paper is informative and very interesting, which evaluate the efficacy of entecavir in the treatment of hepatitis B virus-cirrhosis. Although it does not offer any very novel insights, it does provide worthwhile "real world" data in this group of patients.

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